

REMARKS

Reconsideration of the above-identified application in view of the above amendments and the following remarks is respectfully requested. Applicants note that the present amendment accompanies a Request for Continued Examination and is a submission under 37 C.F.R. § 1.114 that complies with 37 C.F.R. § 1.111. Claims 1, 2, 4-23 are now pending. Claims 9, 12, 16 and 22 have been canceled. Claims 4, 14, 15, 17 and 23 have been amended and claim 26 has been added to more specifically recite certain aspects of the invention. In addition, the specification has been amended to more accurately describe certain aspects of the invention. Support for these amendments may be found throughout the specification and claims as originally filed and does not constitute new matter. Specific support for lipids comprising sphingomyelin and cholesterol in a molar ratio of about 70:30 to about 40:45 is provided, *e.g.*, on page 7, lines 14-15. It should also be noted that the above amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application.

Applicants thank the Examiner for acknowledging priority of the instant application to U.S. Provisional Application Nos. 60/264,616 and 60/215,556, and for withdrawing the rejection under 35 U.S.C. § 101 and the objections to the disclosure and claims.

*Rejection Under Obviousness-Type Double Patenting*

Claims 1-11 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 32-35, 37, 39-57 and 60-63 of co-pending Application No. 09/896,812. Applicants respectfully request that the Examiner continue to hold this rejection in abeyance until allowable subject matter has been identified.

*Rejection Under 35 U.S.C. § 112, Second Paragraph*

Claims 9 and 12 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite with regard to the term "trace amounts." To expedite prosecution of the instant

application and without acquiescence to this basis of rejection, Applicants have canceled claims 9 and 12, thereby obviating this basis of rejection.

Rejection Under 35 U.S.C. § 103(a)

Claims 1, 2 and 4-23 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Slater *et al.* (U.S. Patent No. 6,355,268) and further in view of Nexstar Pharmaceuticals, Inc. (Nexstar; PCT Publication No. WO 99/13816). More specifically, the Examiner asserts that Slater *et al.* discloses liposome-entrapped topoisomerase inhibitors, including camptothecin and topotecan. The Examiner concedes that Slater *et al.* fails to teach the dosage of instant claims 1, 5, 17, 22 and 23, the ratio of sphingomyelin to cholesterol of instant claim 4, and the methods of treatment of instant claims 18-21. However, the Examiner is of the opinion that the skilled artisan would have been able to determine an effective amount, and believes that differences in concentration will not support patentability of subject matter encompassed by prior art unless there is evidence indicating such concentration is critical. In addition, the Examiner alleges that Nexstar teaches phospholipid to cholesterol ratios that overlap those of instant claim 4 and further alleges that Nexstar contemplates a variety of cancers and, therefore, meets the specific methods of treatment of claims 18-21. The Examiner concludes that it would have been obvious to one having ordinary skill in the art at the time the invention was made to have used liposome-encapsulated camptothecin and topotecan as taught by Slater *et al.* to treat the various cancers taught by Nexstar.

Applicants respectfully traverse this basis of rejection and submit that the subject matter of the instant claims is not obvious in light of Slater *et al.* and Nexstar, either alone or in combination. Specifically, Applicants submit that the Examiner fails to establish a *prima facie* case of obviousness.

As an initial matter, Applicants submit that the combination of Slater *et al.* and Nexstar fails to render obvious the claimed invention, since neither Slater *et al.* nor Nexstar teach or suggest the claimed liposomal camptothecin dosages. Rather, Applicants submit that the combination of references teaches away from the claimed dosages, since Slater *et al.* teaches that

greater concentrations are required for efficacy, and Nexstar also does not teach or suggest the use of the claimed dosages.

Applicants submit that although the claimed dosages are expressed as  $\text{mg}/\text{M}^2$ , the skilled artisan would immediately appreciate that these dosages may be readily converted to  $\text{mg}/\text{kg}$ , using conversion factors well known and established in the art, including the dose calculator provided by the U.S. Food and Drug Administration at <http://www.fda.gov/cder/cancer/animalframe.htm> and described in *Cancer Chemother Repts* 50(4):219 (1966). Applicants further note that it is standard practice in the art to use dosage units of  $\text{mg}/\text{kg}$  for animal studies but to convert such dosages to  $\text{mg}/\text{M}^2$  to obtain the human dose equivalent. Accordingly, based upon the instant application and general knowledge in the art, the skilled artisan would clearly understand that the liposomal-topotecan-dosages-recited in claims 1 and 5 are equivalent to dosages of about 0.0033  $\text{mg}/\text{kg}/\text{dose}$  to about 2.5  $\text{mg}/\text{kg}/\text{dose}$  and about 0.33  $\text{mg}/\text{kg}/\text{dose}$  to about 1.33  $\text{mg}/\text{kg}/\text{dose}$ , respectively.

Applicants also submit that the skilled artisan would not be motivated to use liposomal topotecan formulations at the claimed dosage equivalents of about 0.0033  $\text{mg}/\text{kg}/\text{dose}$  to about 2.5  $\text{mg}/\text{kg}/\text{dose}$  (claim 1) and about 0.33  $\text{mg}/\text{kg}/\text{dose}$  to about 1.33  $\text{mg}/\text{kg}/\text{dose}$  (claim 5), in light of the teachings of Slater *et al.* and Nexstar. As acknowledged by the Examiner, neither reference teaches or suggests the claimed dosages. In addition, the cited references teach away from the claimed dosages. Specifically, Slater *et al.*, which is cited as the primary reference, teaches that dosages of 5  $\text{mg}/\text{kg}$  or 8  $\text{mg}/\text{kg}$  both resulted in complete or partial tumor remission in a human HT-29 xenograft tumor model in 10/12 animals tested, while a dosage of 2  $\text{mg}/\text{kg}$  resulted in complete remission in only one animal and partial remission in only two animals of the twelve tested (Table 6). In addition, Slater *et al.* teaches that animals treated with liposome-entrapped topotecan at a dosage of 2  $\text{mg}/\text{kg}$  exhibited tumor growth, while animals treated at dosages of 5  $\text{mg}/\text{kg}$  or 8  $\text{mg}/\text{kg}$  exhibited tumor regression (column 18, lines 7-12). Applicants note that Nexstar fails to remedy this deficiency, since it also fails to teach the claimed dosages. Accordingly, the skilled artisan would conclude that dosages greater than 2  $\text{mg}/\text{kg}$  of liposomal topotecan are required for efficacy, and, accordingly, the claimed dosages would not be obvious in light of the cited references.

Similarly, the skilled artisan would not be motivated by the teachings of Slater *et al.* and Nexstar to use any liposomal camptothecin formulations at the unit dosage equivalents of about 0.005 mg/kg/dose to about 0.33 mg/kg/dose, which corresponds to the unit dosage range recited in claim 23. Again, as acknowledged by the Examiner, neither reference teaches nor suggests the claimed dosages, and the cited references teach away from the claimed dosages. More specifically, Slater *et al.* provides absolutely no evidence that a liposomal camptothecin dosage of less than 0.5 mg/kg would be efficacious. Rather, the data presented in Slater *et al.*, including, *e.g.*, in Table 4, clearly indicates that lower doses exhibit markedly less efficacy and would, therefore, discourage the skilled artisan from using liposomal camptothecins at the dosages recited in claim 23.

Applicants also respectfully submit that the cited references, either alone or in combination, fail to render obvious the claimed liposomal camptothecins comprising a mixture of sphingomyelin and cholesterol, and methods of use thereof, as recited in claims 1, 2, 4-23 and 26, since the skilled artisan would not be motivated by either reference to combine their teachings to achieve the claimed invention. Rather, Slater *et al.* teaches liposomes that include a vesicle-forming lipid derivatized with a hydrophilic polymer to increase drug retention and clinical efficacy (see, *e.g.*, Abstract and column 7, lines 37-38). Regarding the specific lipid components of such liposomes, Slater *et al.* merely provides a list of lipids that might be used according to the invention. Accordingly, Slater *et al.* might motivate the skilled artisan to make a liposome that includes a vesicle-forming lipid derivatized with a hydrophilic polymer, but Slater *et al.* provides no motivation to use the claimed liposomal formulation comprising sphingomyelin and cholesterol. Furthermore, Nexstar fails to remedy this deficiency, as Nexstar does not contemplate the use of liposomes comprising sphingomyelin and thus provides no indication that the inclusion of sphingomyelin in liposomes comprising hydrophilic polymer-derivatized lipids would be advantageous. Accordingly, the skilled artisan would have no motivation to combine these references to achieve the claimed invention.

In addition, Applicants submit that even assuming *arguendo* that each element of the claimed invention was taught by a cited reference, the cited combination of references fails to render the claimed invention obvious, since the references fail to provide the requisite teaching

or suggestion of the desirability of combining the teachings of the references to reach the present invention. Applicants respectfully submit that the mere fact that the teachings of the prior art *can* be combined or modified, or that a person having ordinary skill in the art is *capable* of combining or modifying the teachings of the prior art, does not make the resultant combination *prima facie* obvious, as the prior art must also suggest the desirability of the combination (*see, e.g., In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990); *In re Fritch*, 23 USPQ2d 1780 (Fed. Cir. 1992)). Since neither of the cited references teach or suggest any advantage or desirability of modifying the teachings of the references to produce liposomes comprising sphingomyelin and cholesterol, Applicants submit that the Action fails to establish a *prima facie* case of obviousness.

Applicants further submit that the nonobviousness of the claimed invention is evidenced by the fact that the claimed liposomal camptothecin formulations comprising sphingomyelin and cholesterol offer superior qualities and unexpected advantages as compared to other liposomal camptothecin formulations, and that these advantages were unrecognized by Slater *et al.* and Nexstar. Specifically, the claimed liposomal compositions display increased efficacy at equivalent dosages when compared to the liposomal camptothecin formulations described by Slater *et al.* In addition, the claimed liposomal camptothecin formulations are surprisingly efficacious at low dosages that did not display substantial efficacy for the liposomal camptothecin formulations described in Slater *et al.* Applicants file herewith the Declaration of Sean Semple, M.Sc., which further details the surprising advantages of the presently claimed liposomal camptothecin dosage forms and, thus, provides evidence of the non-obviousness of the claimed invention. Applicants submit that even assuming *arguendo* that a *prima facie* case of obviousness had been established, this evidence is sufficient to rebut the same.

As a final note, Applicants submit that the methods of using the liposomal camptothecins of the present invention presented in claims 13-22 and 26 are not obvious in light of the cited references, since each of these claims recites the use of a liposomal topotecan formulation at a dosage that is not obvious for the reasons discussed above. Furthermore, Applicants note that claims 18-21 and 26 are drawn to methods of treatment using specifically recited internal regimes, which are not disclosed in either Slater *et al.* or Nexstar. In addition,

claim 15 also includes the administration of a treatment for neutropenia or platelet deficiency, which is not described in Slater *et al.* or Nexstar. Accordingly, Applicants submit that these claims cannot be obvious in light of these references and respectfully request that this basis of rejection be reconsidered and withdrawn.

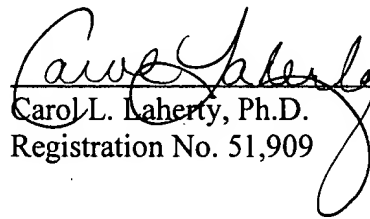
The Commissioner is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants respectfully request allowance of claims 1, 2, 4-23 and 26. A good faith effort has been made to place this application in condition for allowance. However, should any further issue require attention, the Examiner is requested to contact the undersigned at (206) 622-4900.

Respectfully submitted,

Thomas Madden et al.

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Enclosure:

Postcard

Declaration of Sean Semple

Request for Continuation Application (+ copy)

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